Lyme Arthritis and Clinical Judgment

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When a child presents with acute arthritis, the immediate question is whether it is "septic" (acute bacterial) arthritis, which, in addition to antimicrobial treatment, may need surgical washout to prevent permanent damage to the joint. This can be problematic in areas in which Lyme disease is endemic because Lyme arthritis, which does not require surgical washout and typically is subacute, can at times present like septic arthritis.[1] In this issue of *Pediatrics*, Nigrovic et al[2] address the question of whether invasive procedures (diagnostic arthrocentesis and surgical washout) can be avoided in patients who have Lyme arthritis by relying on the result of a C6 enzyme-linked immunoassay (EIA) for serum antibodies against *Borrelia burgdorferi*. The standard approach to diagnose Lyme arthritis is a 2-tier test for serum antibodies. The first-tier test typically is an EIA that uses antigens of sonicated whole *B burgdorferi* organisms to measure the quantity of the patient's antibodies (immunoglobulin M and immunoglobulin G combined) against *B burgdorferi*. However, an EIA result may be positive from cross-reactive antibodies. Consequently, if the EIA result is positive or equivocal, second-tier tests (Western immunoblots, which separately detect immunoglobulin M and immunoglobulin G antibodies against specific surface proteins of *B burgdorferi*) are performed to assess the specificity of the EIA result. It was hoped that newer EIAs that use the C6 peptide, a highly conserved surface lipoprotein of *B burgdorferi*, as the antigen would be both as sensitive as and more specific than the whole-cell EIA. Studies indicate that the C6 EIA has excellent sensitivity, but its specificity, although better than that of the whole-cell EIA, is not as good as that of 2-tier tests.[3]

Nigrovic et al[2] reported on 911 patients who presented with either pain or swelling of a joint and were tested for Lyme disease at 1 of 6 pediatric emergency departments located in areas in which Lyme disease is endemic. The investigators performed C6 EIAs on samples from all of the patients and compared those results with the results of 2-tier testing. The authors report that for Lyme arthritis, a positive or equivocal C6 EIA result had 100% sensitivity, 94% specificity, a positive predictive value of 84%, and a negative predictive value of 100%.

There are several issues with these results. First, the authors' definition of Lyme arthritis required a positive first-tier test result (ie, a positive or equivocal C6 EIA result followed by a positive western immunoblot result). Thus, of course the sensitivity of the C6 assay is 100%, by definition it would have to be. Moreover, the results of the C6 EIAs were not compared with results of a whole-cell EIA. It is not likely that sensitivity of the 2 types of EIAs would be significantly different. Another issue is their estimate of the specificity of the test. Studies have shown that after infection, antibodies against *B burgdorferi* remain present for decades.[4] Hence, in endemic areas, a positive antibody test result could be due to a previous infection and be unrelated to the active arthritis. In addition, more than one-third of the patients with "arthritis" had pain without swelling of the joint. We know that Lyme arthritis is almost always

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associated with an effusion.[5] Thus, the test result likely was falsely positive in many of the children without swelling of the joint. Furthermore, only 11 (1%) of the children in the study had septic arthritis, none of whom had a positive C6 EIA result (100% specificity, but the lower end of the 95% confidence interval for specificity is only 68%).

The authors suggest that by using the C6 EIA result to identify children at low risk of having bacterial arthritis, many of the invasive procedures that these children would otherwise undergo could be avoided. When deciding how to manage a patient with acute arthritis, clinicians should evaluate the entire clinical picture, of which the result of an EIA is only 1 component. In a patient with an acutely inflamed (ie, swollen and exquisitely tender) joint, a diagnostic arthrocentesis is usually indicated regardless of the result of either an EIA alone or even of a 2-tier test for Lyme disease. On the other hand, in a child with potential exposure to ticks (most patients with Lyme disease do not have a history of a recognized tick bite) and a compatible clinical picture, such as subacute arthritis, it is reasonable to defer invasive procedures while awaiting the results of a 2-tier test. The predictive value of either a positive or a negative C6 EIA result is profoundly affected by the probability that the patient has Lyme arthritis before the test is performed ("prior probability").[6,7] Hence, clinical judgment is critical, both for assessing the need to order an antibody test for Lyme disease (it should not be ordered if the prior probability of Lyme disease is low) and for interpreting the results.

ABBREVIATION

EIA: enzyme-linked immunoassay

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